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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/363,100 | 07/29/1999 | DONALD A.G. MICKLE | 50074/004003 | 7723 |

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| EXAMINER |
|---|
| AFREMOVA, VERA |

| ART UNIT | PAPER NUMBER |
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| 1651 | |

DATE MAILED: 07/02/2002 18

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/363,100 | Applicant(s) Mickle et al. |
|---|---|---|
| | Examiner Vera Afremova | Art Unit 1651 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Apr 16, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1, 2, 4-11, and 13-28* is/are pending in the application.

4a) Of the above, claim(s) *14-24* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-11, 13, and 25-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 17
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1, 2, 4-11, 13 and 25-28 as amended are under examination in the instant office action. [Paper No. 16 filed 4/16/2002].

Claims 14-24 were withdrawn from further consideration pursuant to 37CFR 1.142(b) as being drawn to nonelected inventions. Claims 3,12,29 and 30 were canceled by applicants. [Paper No. 16 filed 4/16/2002].

### *Claim Rejections - 35 USC § 112*

### *Indefinite*

Claims rejected under 35 U.S.C. 112, *second paragraph*, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 25 as amended are rendered indefinite by the phrases "repairing" scarred myocardial tissue and scar tissue "repairs" in the lack of definitions in the specification as field. It is unclear what is regarded as "repairs" and what is achieved by "repairing" as presently claimed.

### *New matter*

Claims 1, 2, 4-11, 13 and 25-28 as amended are rejected under 35 U.S.C. 112, *first paragraph*, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitations such as "repairing scarred myocardial tissue" and "scar tissue repairs" has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of the use of "repairing scarred myocardial tissue" and "scar tissue repairs". There is exemplified disclosure directed to improvement of cardiac function in rats with myocardial scars (example II) and in porcine model (example III). However, this is not sufficient support for the new genus, such as "repairing scarred myocardial tissue" and "scar tissue repairs", because it is uncertain what is the difference between cardiac function improvement which is disclosed and "repairs" or "repairing" which is claimed. This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of limitation drawn to "repairing scarred myocardial tissue" and "scar tissue repairs" is considered to be the insertion of new matter for the above reasons.

***Claim Rejections - 35 U.S.C. § 102***

The rejection of claims under 35 U.S.C. 102(b) as being anticipated by US 5,736,396 [A] has been withdrawn because the cited patent does not clearly point out a particular site for

administration/injection of mesenchymal cells committed to myogenic differentiation, such as "myocardial scar tissue" as presently claimed, by the way of a particular example but it rather teaches a generic administration site in need of mesenchymal cells committed to a lineage of choice, including myogenic lineage, for treating a patient in need thereof. (col. 2, lines 1-20; col. 1, line 60; example 5).

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-11, 13 and 25-28 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,602,301 [IDS-10-8], Robinson et al. [U], Murry et al. [IDS-10-31] and/or WO 99/03973 [IDS-13-1] taken with Wakitani et al. [IDS-10-37] and US 5,736,396 [A].

Claims are directed to a method for repairing scarred myocardial tissue wherein the method comprises a step of administering to myocardial scar tissue a cellular suspension containing mesenchymal stem cells (MSC) wherein administration of said cells to said myocardial tissue repairs said scarred myocardial tissue. Some claims are further drawn to the use of mesenchymal cells isolated from bone marrow and to inducing differentiation of mesenchymal cells by exposing cells to 5-azacytidine or analogs thereof at concentration of 1-100 μM or 10 μM. Some claims are further drawn to culturing the mesenchymal cells for 7 days. Some claims are further drawn to the use of MSC which were not passaged.

The cited references are relied upon as explained in the prior office action and repeated herein.

US 5,602,301 [IDS-10-8] teaches a method for administrating of cells of myogenic lineage such as skeletal myoblasts or cardiomyocytes into myocardial tissues of living mammals (col. 3, lines 41-43).

Robinson et al. [U] teach a method for treating a heart failure or injured myocardial tissue by implantation into the myocardial tissues of cells of myogenic lineage such as immature muscle myoblasts in order to generate new muscle within injured cardiac tissue (pages 81-82, for example).

Murry et al. [IDS-10-31] teach a method for repairing myocardial tissues by transplanting into injured or scarred myocardial tissues of cells of myogenic lineage such immature or neonatal skeletal myoblasts (see abstract, for example).

WO 99/03973 [IDS-13-1] discloses a method for administering to the heart tissues a cardiomyocytes producing amount of MSC (see abstract, for example) and regeneration of heart tissues using MSCs (example 2).

The cited US 5,602,301 [IDS-10-8], Robinson et al. [U], Murry et al. [IDS-10-31] and/or WO 99/03973 [IDS-13-1] are relied upon for the teaching of methods for treating myocardial disorders by administering into myocardial tissues, including damaged or injured myocardial tissues, of cells belonging to myogenic lineage, including mature cells of myogenic lineage, unmature cells of myogenic lineage and progenitor cells such as MSCs. The cited references are

lacking particular disclosure related to treating cells of myogenic lineages with 5-azacytidine or analogs thereof to promote myogenic differentiation.

However, the reference by Wakitani et al. [IDS-10-37] teaches treating cells of myogenic lineage such as MSCs with 5-azacytidine or analogs thereof and it suggests the use of treated MSC for transplantation and myogenic regeneration (see abstract). The cited reference also teaches the advantage of using MSC as a myogenic precursor over the use of differentiated myoblasts for the purpose of transplantation and surgery. The use of ex-vivo expanded and pretreated MSC is a more efficient procedure as compared to the large biopsy necessary to obtain myoblasts from autologous sites for treating a massive muscle defect. (page 1425, last par.).

The cited patent US 5,736,396 [A] also teaches that use of MSC, which are derived from bone marrow and treated with 5-azacytidine or analogs thereof, as a composition suitable for administration in a method for treating tissues disorders with mesenchymal stem cells committed to a lineage of choice, including myogenic lineage, for treating a patient in need thereof. (col. 2, lines 1-20; col. 1, line 60; example 5).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute cell compositions of the secondary references such as bone derived MSC treated with 5-azacytidine or analogs thereof prior to administration for the myoblast cell compositions of the primary references in the method for treating myocardial tissues with a reasonable expectation of success of transplantation and cell regeneration because the prior art teaches treating myocardial disorders by administering into myocardial tissues,

including damaged or injured myocardial tissues, of cells belonging to myogenic lineage, including mature cells of myogenic lineage, unmature cells of myogenic lineage and progenitor cells such as MSCs. One of skill in the art would have been motivated to use MSCs as myogenic precursor cells because MSCs are advantageous over myoblast compositions which require large muscle biopsy, for example, as taught by Wakitani et al. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. 103.

***Response to Arguments***

Applicants' arguments filed 4/16/2002 have been fully considered but they are not persuasive.

Applicants' main argument appear to be directed to the idea that "none the cited references teaches or suggests transplanting cells of any kind into myocardial scar tissue" (response page 5, last par.).

Upon review of the references it is not found true.

For example: The reference by Robinson et al teaches transplanting or introducing of immature myoblasts into "injured cardiac tissue" (page 81, par. 1) which is a scarred myocardial tissue as the result of cryoinjury (page 81, par. 1, lines 3-line 10). The same model is used by applicants such as myocardial scars generated by cryoinjury (specification page 16).

The reference by Murry et al. also teaches teach transplanting of neonatal myoblasts into myocardial scar tissues or into scarred tissues obtained by cryoinjury (see page 2113, at section "injury models"). Moreover, this reference demonstrates that both transplantation protocols, such as transplantation immediate after injury and transplantation 1 week after injury, yielded similar results. The model of one week old scarred tissue is used to mimic a clinical situation. (See page 2514, col. 1, par. 3).

Myocardial injury is healed by scarring (see first line of abstract by Murry et al.). Therefore, all cited references encompass transplantation into myocardial scar tissue of cells belonging to myogenic lineage including mature myoblasts, unmature myoblasts as well as MSC either uncommitted (untreated or "non-passaged") or committed to myogenic lineage (treated with 5-azacytidine or analogs thereof to induce myogenic differentiation). The cited references also teach and demonstrate regeneration of myocardial tissue as result of transplantation.

No claims are allowed.

## *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

June 25, 2002.

Irene Marx

IRENE MARX

PRIMARY EXAMINER